University of Sistan and Baluchestan

Journal of Epigenetics

Online ISSN: 2676 - 4350

Homepage: https://jep.usb.ac.ir

Iranian Genetics Society

A Novel Pathogenic Variant of GDAP1 Gene in a Patient with Charcot-Marie-Tooth disease type 2: A Case Report

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ARTICLE INFO

Article type:
Research Article

Article history:
Received: 6 December 2023
Revised: 27 December 2023
Accepted: 30 December 2023

Keywords:
CMT,
GDAP1,
WES,
Proband,
Sanger.

A B S T R A C T

Background

Charcot Marie Tooth disease type 2 group are characterized by signs of axonal degeneration in the absence of obvious myelin alterations, normal or slightly reduced nerve conduction velocities, and progressive distal muscle weakness and atrophy. Charcot Marie Tooth disease type 2k onset is in early childhood (younger than 3 years). This phenotype is characterized by foot deformities, kyphoscoliosis, distal limb muscle weakness and atrophy, areflexia, and diminished sensation in the lower limbs. Weakness in the upper limbs is observed in the first decade, with clawing of the fingers. Inheritance can be autosomal dominant or recessive.

Method

we sequenced the entire coding region and exon-intron boundaries of the GDAP1 gene in one individual using whole-exome sequencing (WES). Co-segregation analysis was also performed in the proband and mother using Sanger sequencing (the mother has incomplete penetrance). In addition, bioinformatics analyzes were performed to predict the probability and pathogenicity of the mutation.

Results

In exon 6 of the GDAP1 gene, a novel deleterious heterozygous mutation c.830A > G; p. E277G was identified.

DOI: https://doi.org/ 10.22111/JEP.2023.47369.1062

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Publisher: University of Sistan and Baluchestan

How to Cite: Rafiee Komachali, S., Khaje, A., Nakhaee- Moghadam, M., Kordi Tamandani, B,. & Kordi Tamandani, D,. (2024). A Novel Pathogenic Variant of GDAP1 Gene in a Patient with Charcot-Marie-Tooth disease type 2: A Case Report. *Journal of Epigenetics*, 5(1), 1-4. https://doi.org/ 10.22111/JEP.2023.47369.1062

Conclusions

We surveyed the clinical and genetic features of this patient and recognized a novel pathogenic variant c.830A > G; p. E277G in the GDAP1 gene. according to the patient's symptoms, we identified a new type of pathogen. This is a missense mutation and its inheritance is autosomal dominant.

Introduction

Hereditary sensory-motor neuropathy (HMSN), which is also known as Charcot Marie Tooth disease or peroneal muscular atrophy (Mersiyanova et al., 2000), is a clinically and genetically heterogeneous group of diseases for which more than 100 genes or loci have been identified (Higuchi et al., 2016), and all of them are basically Weakness and progressive atrophy of the distal muscles are noted (Mersiyanova et al., 2000).

Clinical classification based on electrical conduction velocity (MNCV) is divided into two types. Type 1, which has a demyelinating state and is associated with hypertrophic changes and onion bulb formation in nerve biopsy and type 2 is the axonal condition in which the MNCV is normal or partially reduced (Berciano et al., 2017).

The autosomal dominant type of CMT, which is the most common form of the disease, slowly and progressively weakens the distal muscles, and the motor powers of the lower limbs (legs) are lost between the ages of 10 and 30 years. The same thing happens in the hands at older ages and is usually accompanied by ataxia and muscle tremors. People's legs look like an upside down bottle (Banchs et al., 2009).

Mobility of patients becomes difficult with increasing age and the legs lose their natural arch and a condition known as Pes cavus is created in them. The age of onset of CMT type 2 is later than type 1 and the course of the disease is milder, so that some patients show very few symptoms (Bombelli et al., 2014).

Charcot Marie Tooth type 2 is genetically very heterogeneous and about 20% of cases occur due to variants in the mitomyosin gene (MEN2), which is a nuclear gene and encodes an abnormal mitochondrial splicing/dissociating protein. Other genes that are seen in CMT type 2 and have pathogenic variants include NEFL, GDAP1, GARS and YARS, and as a result of them, intermediate demyelinating symptoms and axonal neuropathy are seen (Larrea et al., 2019).

Mutations in the ganglioside-induced differentiation-associated-protein 1 gene (GDAP1), which encodes a protein anchored to the mitochondrial outer membrane, are usually associated with the recessive forms of CMT disease and only rarely with the autosomal dominant forms. The function of GDAP1 is not fully understood but it plays a role in mitochondrial dynamics by promoting fission events (Cassereau et al., 2011).

At the neuronal level, GDAP1 mutations may lead to perturbed axonal transport and impaired energy production as in other neurodegenerative diseases due to mutations in genes involved in mitochondrial dynamics (Miressi et al., 2021).

Clinical presentation

CMT disease corresponds to a group of genetically heterogeneous disorders that share clinical characteristics including weakness of distal limb muscles, especially involving the peroneal compartment, whence its former appellation of peroneal muscular atrophy. These characteristics are usually associated with distal sensory loss, skeletal deformities, and decrease or absence of deep tendon reflexes. The longer muscle fibers, which are affected earlier and more severely than the shorter fibers (Cassereau et al., 2011).

Materials and method

The present study involves an 18-year-old boy who has symptoms such as mental disorder, developmental and brain disorders, walking disorder, speech disorder, learning disability and hyperactivity. As a result of genetic counseling, the proband's parents did not show any sympt. Informed consent was obtained from all human adult participants and from the parents or legal guardians of minors in the Dr. Kordi's laboratory of Zahedan. In this study, internal consent has been prepared, adjusted, and available in the Dr. Kordi's laboratory of Zahedan (Figure 1).

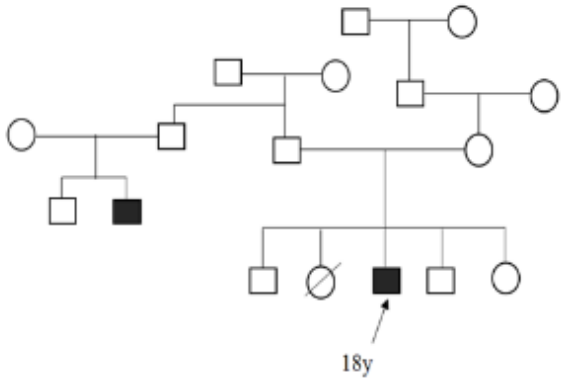


Figure 1: Pedigree of the proband

Genome DNA was extracted from peripheral whole blood sample the patient and whole exome sequencing was done on illumina nonaseq6000 platform with 150x depth of coverage and 151bp paired end reads. raw sequence data analysis, including base calling, alignment to the hg19 human reference genome (genome reference consortium GRCh37) and variant was performed.

We sequenced the entire coding region and exon-intron boundaries of the GDAP1 gene in one individual using whole-exome sequencing (WES). Co-segregation analysis was also performed in the proband and mother using Sanger sequencing (the mother has incomplete penetrance). In addition, bioinformatic analyzes were performed to predict the probability and pathogenicity of the mutation.

Results

Performing WES on proband identified a novel likely pathogenic c.830A>G/ p.E277G mutation in GDAP1 gene locates on 8q21.11. This gene has AD inheritance. His mother also sanger sequencing confirmed that he is heterozygote in the mentioned locus but considering that he has incomplete penetrance, no symptoms were observed in his mother. With the confirmation, it is obvious that inheritance is AD in the mentioned family, the likely pathogenic c.830A>G/ p.E277G mutation is approved.

Discussion

Based on the results, our proband that is heterozygote for c.830A>G/ p.E277G as a novel mutation of the GDAP1 gene, is a likely pathogenic variant that has a great risk factor for charcot marie tooth disease type 2 group disease. Identified a heterozygous mutation in the GDAP1 gene in a Korean father and daughter with autosomal dominant adult-onset axonal CMT2K. The phenotype was milder than that usually observed in patients with recessive GDAP1 mutations (Chung et al., 2008; Pezzini et al., 2016).

Patients with AD *GDAP1* mutations are very rare (Zimoń et al., 2011)because the GDAP1 gene is expressed in Schwann cells and neurons, it is associated with a wide spectrum of neuropathologic abnormalities, leading to the possible existence of several types of CMT, such as axonal, demyelinating, or intermediate AR CMT (Pezzini et al., 2016; Senderek et al., 2003). Most AR CMT patients with the GDAP1 gene mutation show a very early disease onset, usually during infancy, with a severe phenotype that can include vocal cord paresis, diaphragmatic paralysis, or kyphoscoliosis (Stojkovic et al., 2004). However, in our study, which shows the autosomal dominant form of Charcot-Marie-Tooth disease with GDAP1 mutation, the onset of the disease was from the age of 2 years, and the symptoms of the disease were mild.

Conflict of interests

The authors declared no conflict of interests.

Acknowledgements

The authors would like to thank the participants as well as the Dr. Kordi's laboratory of Zahedan.

Ethical considerations

Informed consent was obtained from all human adult participants and from the parents or legal guardians of minors in the Dr. Kordi's laboratory of Zahedan.

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